et al."), both in further view of U.S. Patent No. 5,391,381 ("Wong *et al.*") and U.S. Patent No. 4,404,183 ("Kawata *et al.*"). For the reasons set forth herein, the rejection is overcome.

THE INVENTION

The present invention relates to a timed-release compression-coated formulation. The composition comprises: a) a core tablet comprising a drug and a freely erodible filler, wherein the core tablet is capable of approximately 40 to approximately 90% erosion; and b) an outer layer, wherein the outlayer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein the outer layer optionally contains a drug. By releasing a drug after a specific lag time, it is possible to effectively deliver a drug to a specific site in the digestive tract. In certain aspects, it is useful as a timed-release solid composition for oral administration of a drug that is to be effectively delivered in high concentrations to the afflicted site in the lower digestive tract, a drug that is effectively absorbed in the lower digestive tract, a drug that is effective for chronopharmacotherapy, and the like.

REJECTION UNDER 35 U.S.C.§ 103(a)

Claims 1-26 have been rejected under 35 U.S.C.§ 103(a) as allegedly being obvious over EP 0661045 ("Nakashima *et al.*") in view of EP 0709386 ("Taniguchi *et al.*"), both in further view of U.S. Patent No. 5,391,381 ("Wong *et al.*") and U.S. Patent No. 4,404,183 ("Kawata *et al.*"). According to the Office Action, Nakashima *et al.* disclose a compression-molded tablet comprising a hydrogel-forming polymer and a hydrophilic base. The Office Action acknowledges that Nakashima *et al.* do not disclose an erodible core. However, according to the Office Action, since Nakashima *et al.* disclose a core that contains polyethylene glycol, a substance allegedly suitably erodible for the present invention, the Office Action alleges that Nakashima *et al.* render the present invention obvious. In addition, the Office Action alleges that Nakashima *et al.*, in combination with Kawata *et al.*, Wong *et al.*, and Taniguchi *et al.* render each of the

claims of the present invention obvious. In response, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.
>
> *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

All three elements set forth above must be present in order to establish a prima facie case of obviousness. Applicants assert that a prima facie case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Office Action has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The present invention relates to a timed-release compression-coated formulation. Timed-release means, for example, that after a specific lag, the drug from

the pharmaceutical preparation is released. In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. The core tablet comprises the active ingredient and a freely erodible filler, and the outer layer comprises a hydrogel-forming polymer substance and hydrophilic base (*see*, Exhibit 1). Importantly, the core tablet is capable of approximately 40 to approximately 90% erosion. Surprisingly, Applicants have found that a percentage erosion of the core tablet of approximately 40 to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability (see, page 4, lines 16-24 of the specification). Before the present invention, the requirement for 40 to approximately 90% erosion to obtain an ideal timed-release pharmaceutical preparation was ***unknown***.

With reference to Exhibit 2, the composition of the present invention is characterized by the following criteria: a) it absorbs the water in the upper digestive tract so that the outer layer all but completely gels; b) the water penetrates into the core tablet, and a solution state or suspension state is produced once the core tablet has been eroded prior to the outer layer disintegrating; c) the gelled outer layer is eroded as it moves to the lower digestive tract; and d) part of the outer layer is disintegrated or peeled, thus releasing the drug. Advantageously, ideal timed release of a drug can be achieved by this type of structure having a specific percentage erosion of the core tablet, even in the lower digestive tract with a low water content.

In contrast, Nakashima *et al.* teach a hydrogel sustained-release pharmaceutical preparation made from drug, hydrophilic base, and hydrogel-forming polymer substance with which good drug release is possible in the upper digestive tract as well as the colon of the lower digestive tract (see, page 2, lines 16-20 of the specification). However, Nakashima *et al.* do not disclose an erodible core as presently taught and claimed. Applicants have discovered that the combination of a) adjusting the components in the core tablet, thereby controlling the percent erosion of the core tablet, and b) varying the mixture ratio of components in the outer layer is effective for achieving ideal timed release of a drug. For example, the addition of polyethylene glycol of high solubility in water to the core tablet is effective and that ***timed release*** can be

adjusted by varying the mixture ratio of polyethylene glycol and polyethylene oxide in the outer layer. Examples in the specification teach various ratios of polyethylene glycol and polyethylene oxide suitable for preparing one formulation of the present invention. Nakashima *et al.* do not teach or suggest that the core tablet is capable of approximately 40 to approximately 90% erosion, which is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability. Nakashima *et al.* teach the use of a hydrophilic base (*see*, page 6, lines 38-42 of Nakashima *et al.*) wherein the ratios are different than those of the present invention. Therefore, Nakashima *et al.* do not teach or suggest the timed-release compression coated formulations of the present invention. Furthermore, there is no suggestion or motivation to modify the references so that the core tablet is capable of approximately 40 to approximately 90% erosion. Prior to the advent of the present invention, it was not known that these percentages of erosion were necessary for the preparation of ideal timed-release pharmaceutical preparation having high bioavailability. Thus, one of skill in the art would not have been motivated to modify the teachings of Nakashima *et al.* to arrive at the present invention. As such, Applicants respectfully request that the rejection be withdrawn.

2. There is No Reasonable Expectation of Success

In addition, there is no reasonable expectation of success that the modification that the Office Action contemplates will succeed. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

The Office Action suggests that it would have been obvious to one of skill in the art to modify the compositions of Nakashima *et al.* by including red and/or yellow ferric oxide. In response, Applicants respectfully traverse the rejection.

As discussed above, Nakashima *et al.* teach a hydrogel sustained-release pharmaceutical preparation made from drug, hydrophilic base, and hydrogel-forming polymer substance. Nakashima *et al.* do not disclose an erodible core as claimed by the present invention. Furthermore, Nakashima *et al.* do not teach or suggest that the core

tablet is capable of approximately 40 to approximately 90% erosion, which is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability.

The invention of Wong *et al.* relates to patterned drug delivery, including timed-release. Although Wong *et al.* disclose tablet preparations including a polyethylene oxide and a red ferric oxide for coloring, the use of red and/or yellow ferric oxide for avoiding acceleration of the dissolution of a drug, as disclosed in the present invention, is ***not*** common in the art (*see*, page 18, lines 20-25 of the specification). Thus, one of skill in the art would ***not*** have been motivated by Wong *et al.* to include red and/or yellow ferric oxide in the compositions of Nakashima *et al.* in order to stabilize release properties of the drug. Furthermore, inclusion of red and/or yellow ferric oxide in the formulations taught by Nakashima *et al.* would not result in success, since the combination would not suggest the present invention, which requires that the core tablet is capable of approximately 40 to approximately 90% erosion. Similarly, the modifications suggested in the Office Action with regard to Taniguchi *et al.* and Kawata *et al.* would ***not*** be expected to succeed, since they rely on the base composition of Nakashima *et al.*, which as stated above, does not comprise a core tablet capable of approximately 40 to approximately 90% erosion. Thus, there is no reasonable expectation of success that the modifications that the Office Action contemplates will succeed, and, as such, Applicants respectfully request that the Examiner withdraw the rejection.

3. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

The present invention claims timed-release compression-coated formulations. Claim 1 sets forth the following:

1. A timed-release compression-coated solid composition for oral administration, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, ***wherein said core tablet is capable of approximately 40 to approximately 90% erosion***; and

b) an outer layer, said outlayer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said outer layer optionally contains a drug.

As discussed above, Applicants surprisingly discovered that a percentage erosion of the core tablet of approximately 40 to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability (*see*, page 4, lines 16-24 of the specification).

Nakashima *et al.* teach a hydrogel sustained-release pharmaceutical preparation made from drug, hydrophilic base, and hydrogel-forming polymer substance. Nakashima *et al.* do not teach or suggest a core tablet capable of approximately 40 to approximately 90% erosion. Therefore, Nakashima *et al.* do not teach or suggest the timed-release compression-coated formulations of the present invention.

Kawata *et al.* disclose a sustained release pharmaceutical composition comprising (i) an amorphous drug such as nicardipine or a salt thereof, or indomethacine or a salt thereof, and the like, (ii) polyethylene oxide (PEO) and (iii) at least one basic substance such as HPMC and the like. Kawata *et al.* do not teach or suggest a core tablet capable of approximately 40 to approximately 90% erosion. Therefore, Kawata *et al.* do ***not*** supplement the deficiencies of Nakashima *et al.*

Wong *et al.* disclose patterned drug delivery. The tablet preparations of Wong *et al.* include red ferric oxide for coloring. Wong *et al.* do not teach or suggest a core tablet capable of approximately 40 to approximately 90% erosion. Therefore, Wong *et al.* do ***not*** supplement the deficiencies of Nakashima *et al.*

Taniguchi *et al.* teach a fused benzazepine derivative and pharmaceutical compositions containing the benzazepine derivative. Taniguchi *et al.* do not teach or suggest a core tablet capable of approximately 40 to approximately 90% erosion.

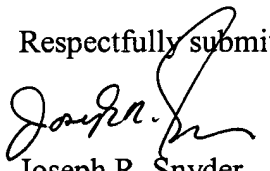
Therefore, Taniguchi *et al.* do ***not*** supplement the deficiencies of Nakashima *et al.* Thus, Applicants respectfully request that the Examiner withdraw the rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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PENDING CLAIMS

1. A timed-release compression-coated solid composition for oral administration, said composition comprising:

a) a core tablet comprising a drug and a freely erodible filler, wherein said core tablet is capable of approximately 40 to approximately 90% erosion; and

b) an outer layer, said outlayer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein said outer layer optionally contains a drug.

2. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the outer layer comprises a drug and wherein the outer layer essentially does not contain the same drug as the core tablet drug.

3. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein there is approximately 75 wt% or less of said drug, approximately 5 to approximately 80 wt% freely erodible filler, approximately 10 to approximately 95 wt% hydrogel-forming polymer substance, and approximately 5 to approximately 80 wt% hydrophilic base.

4. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose.

5. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

6. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler for a basic drug is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid.

7. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the freely erodible filler for an acidic or neutral drug is 1 or 2 or more selected from the group consisting of polyethylene glycol, sucrose or lactulose.

8. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the hydrogel-forming polymer substance contains at least one type of polyethylene oxide.

9. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the hydrogel-forming polymer substance is 1 or 2 or more having a viscosity-average molecular weight of 2,000,000 or higher and/or a viscosity in an aqueous 1% solution (25°C) of 1,000 cp or higher.

10. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the core tablet contains hydrogel-forming polymer substance.

11. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the hydrophilic base is 1 or 2 or more having solubility such that the amount of water needed to dissolve 1 g base is 5 mL or less.

12. The timed-release compression-coated solid composition for oral administration according to claim 11, wherein the hydrophilic base is 1 or 2 or more selected from the group consisting of polyethylene glycol, sucrose, and lactulose.

13. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the hydrogel-forming polymer substance is at least 1 type of polyethylene oxide and further contains red ferric oxide and/or yellow ferric oxide.

14. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug is brought to be effectively released or absorbed in the lower digestive tract.

15. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug is brought to be effective for chronopharmacotherapy.

16. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug is metabolized by cytochrome P-450.

17. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein a drug has the effect of inhibiting metabolism by cytochrome P-450.

18. The timed-release compression-coated solid composition for oral administration according to claim 16, wherein the drug is metabolized by CYP3A4.

19. The timed-release compression-coated solid composition for oral administration according to claim 17, wherein the drug has the effect of inhibiting metabolism by CYP3A4.

20. The timed-release compression-coated solid composition for oral administration according to claim 1, wherein the drug is 4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)carbonyl]-2-phenylbenzanilide or its salt.

21. A method of timed release of a drug, whereby the composition in claim 1 is orally administered.

22. A method for alleviating undesirable drug interaction between a drug and other drugs used concomitantly that employ the same route for drug absorption, distribution, metabolism or excretion *in vivo* in humans, whereby the composition in claim 1 is orally administered.

23. A method of alleviating undesirable drug interaction with between a drug having the effect of inhibiting drug metabolism *in vivo* in humans and another drug according to claim 20 used concomitantly, whereby the composition in claim 1 is used.

24. In a hydrogel-forming compression-coated solid pharmaceutical preparation comprising: a core tablet containing drug and outer layer made from hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition according to claim 1.

25. In a hydrogel-forming compression-coated solid pharmaceutical preparation comprising:

a core tablet containing drug and outer layer made from hydrogel-forming polymer substance and hydrophilic base, the improvement which comprises a timed-release compression-coated solid composition for oral administration, said composition comprising:

(1) a drug and freely erodible filler are mixed with the core tablet;

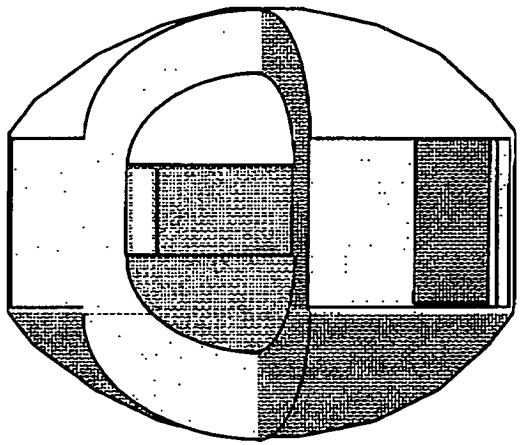
(2) the percentage erosion of the core tablet is approximately 40 to approximately 90%; and

(3) the outer layer essentially does not contain the same drug as the above-mentioned drug.

26. The timed-release compression-coated solid composition for oral administration according to claim 25, wherein the drug is 4'-[(2-methyl-1,4,5,6-tetrahydroimidazo[4,5-d][1]benzazepin-6-yl)carbonyl]-2-phenylbenzanilide or its salt.

EXHIBIT 1

Fig.1 Composition of Formulation



(cross section)

- ✓ *core part with*
  - *drug*
  - *freely erodible filler*
- ✓ *outer layer with*
  - *hydrogel-forming polymer*
  - *hydrophilic base*

Fig.2 Schematic description of gelling and drug release of TR in gastrointestinal tract

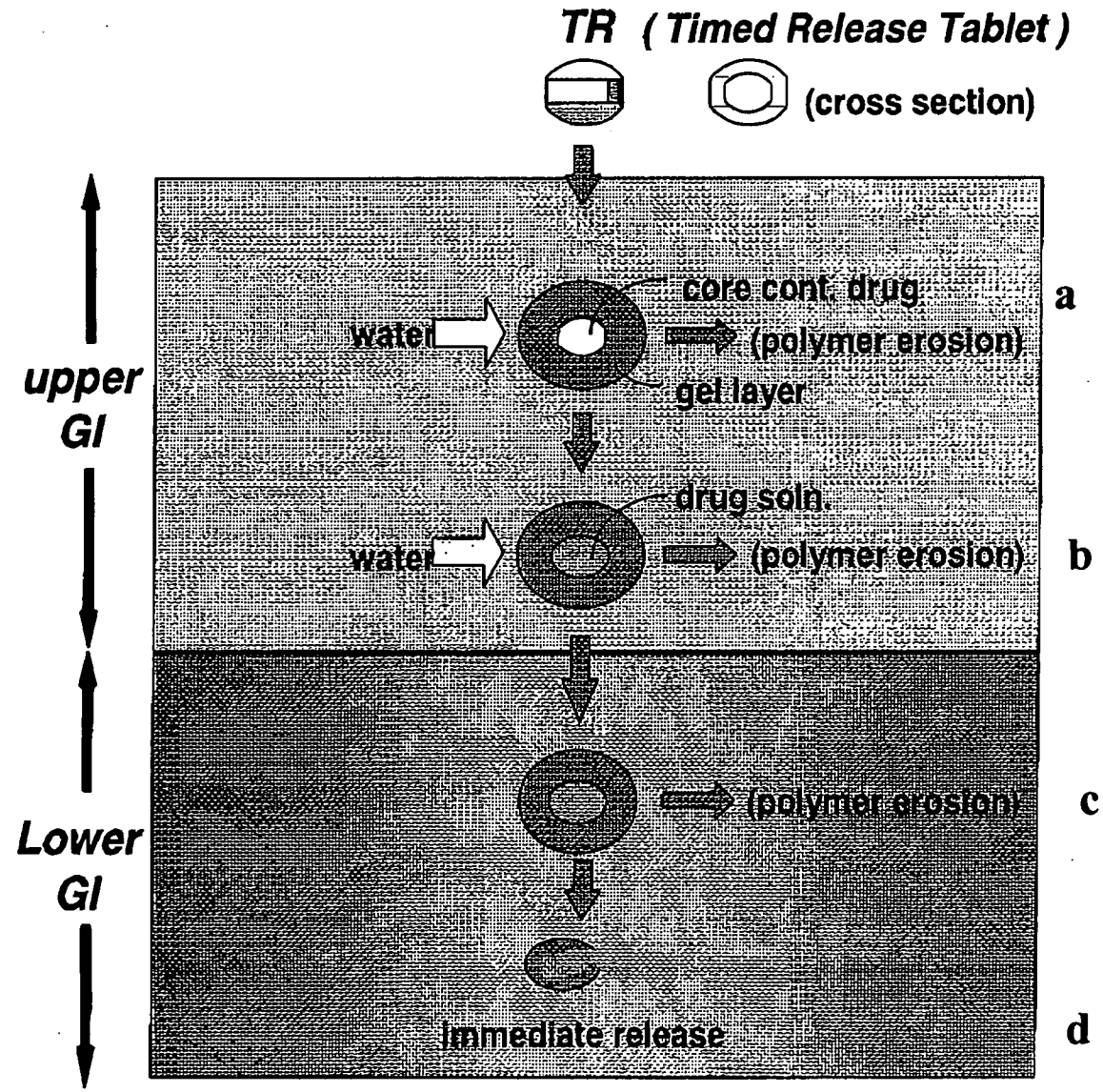


EXHIBIT 2